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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/623,138	08/28/2000	Shigeru Kinoshita	KINOSHITA3	9673

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EXAMINER
HUI, SAN MING R

ART UNIT	PAPER NUMBER
1617	13

DATE MAILED: 04/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/623,138	Applicant(s) KINOSHITA, SHIGERU	
	Examiner San-ming Hui	Art Unit 1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE _____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11,14,15,17,19 and 20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,14,15,17,19 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 29, 2002 has been entered.

The amendments filed October 29, 2002 and January 21, 2003 have been entered.

The outstanding objection of claim 14 under 37 CFR 1.75(c) and claims 17, 19, and 20 under 35 USC 112, first paragraph are withdrawn in view of the amendments filed October 29, 2002 and January 21, 2003.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11, 14-15, 17, and 19-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In the instant case, the specification does not allow one skilled artisan to practice

herein claimed the method of preventing ocular inflammation such as phlyctenular keratitis, corneal infiltration, and keratoconjuctivitis. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence of absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art

7) the predictability of the art, and

8) the breadth of the claims.

The breadth of the instant claims is very broad that the herein claimed method encompasses the prevention of all ocular inflammation. As Hingorani et al. discloses the ocular inflammation would include disorders range from non-sight-threatening inflammation such as seasonal allergic conjunctivitis, perennial allergic conjunctivitis, and giant papillary conjunctivitis, to sight-threatening inflammation, such as vernal keratoconjuctivitis and atopic keratoconjunctivitis (See Hingorani et al., page 209, col. 1, first paragraph). Furthermore, as for the state of the art, Hingorani et al. teaches that the underlying immune mechanism of ocular allergic response is not yet fully elucidated, although some offending

agents are identified (See page 209, col. 1, second paragraph). It is clear from the evidence of Hingorani et al. that the ability to prevent all ocular inflammation is highly unpredictable. Additionally, Applicant fails to provide information or guidance allowing the skilled artisan to ascertain the preventive embodiments without undue experimentation. In the instant case, no working examples with regards to prevention of ocular inflammation are set forth, thereby failing to provide sufficient working examples. The specification also fails to provide information and guidance as to selecting patients whom will likely develop ocular inflammation so that prevention of ocular inflammation would be effected. The pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. Knowing the unpredictability of the art and the lack of sufficient guidance, information, and working examples set forth in the instant specification, one of skilled in the art would be require to perform an undue experimentation for searching the embodiments suitable to practice such a broad invention as herein claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 11, 14-15, 17, and 19-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paul (Fundamental Immunology, 3rd ed., 1993, Raven Press, page 119-121), Niederkorn et al. (Abstract of Reg. Immunol., 1989 ; 2(2) : 83-90), Dam et al. (Journal of Investigational Dermatology Symposium proceedings; 1996;1(1):72-77) and Muller et al. (Journal of Investigational Dermatology Symposium proceedings; 1996;1(1): 68-71) in view of Itoh et al. (WO96/29079, the English translation, Patent US 6,248,732, is also provided), and Hingorani et al. (Drugs 1995; 50(2); 208-221), references of record in the previous office action mailed July 30, 2002.

Paul teaches Langerhans cells (LC) is an antigen presenting cells that is highly effective in presenting antigen to T cells (See page 120, col. 1). Paul also teaches that IL-1 increases the antigen presenting function of LC to T cells (See page 120, col. 1, fifth paragraph).

Niederkorn et al. teaches that LC is present in corneal epithelium and could migrate to the central cornea upon irritants or the presence of IL-1 (See the abstract).

Dam et al. also teaches calcitriol or calcipotriol inhibit TNF-α, a factor which can induce migration of LC, which is a type of antigen presenting cell (See page 76, col. 1, second paragraph). Dam et al. teaches calcitriol and calcipotriol are useful to suppress the number of LC when applied topically (See particularly page 72, col. 2, last paragraph). Dam et al. also teaches calcitriol and calcipotriol suppress the T-cell proliferation (See page 75, col. 2, first paragraph).

Muller et al. teaches the calcitriol inhibits the production of interleukin-1 at a presecretory level such as reducing the levels of interleukin-1α mRNA, which is known to activate lymphocytes (See page 68, col.2, third paragraph).

The references do not expressly teach calcitriol is in a form of ophthalmic solution. The references do not expressly teach calcitriol is useful in treating keratoconjuctivitis, phlyctenular keratitis, or corneal infiltration. The references do not expressly teach calcitriol is useful in a method to inhibit interleukin-1 production in cornea epithelium and thereby treat ocular inflammation.

Itoh et al. teaches that calcitriol can be formulated into an ophthalmic composition (See See particularly col. 11, line 5-10).

Hingorani et al. teaches atopic keratoconjunctivitis is a T-cell inflammation prominent disorder (See particularly abstract). Hingorani et al. also teaches atopic keratoconjunctivitis may lead to infiltration and corneal involvement such as epithelial keratitis (See particularly page 210, col. 1, last paragraph).

It would have been obvious to one skill in the art when the invention was made to employ calcitriol, in ophthalmic solution dosage form, in a method to treat keratoconjuctivitis, phlyctenular keratitis, or corneal infiltration. It would have been obvious to one skill in the art when the invention was made to employ calcitriol in a method to inhibit interleukin-1 production in cornea epithelium and thereby treat ocular inflammation, which is the obvious therapeutic benefit herein recited.

One of ordinary skill in the art would have motivated to employ calcitriol, in ophthalmic solution dosage form, in a method to treat keratoconjuctivitis,

phlyctenular keratitis or corneal infiltration. It is known that calcitriol inhibits the production of LC migration inducing agent, TNF-α. Employing agents that can block the LC migration, such as calcitriol, to the inflammation site, such as in the cornea, and treating keratoconjuctivitis would be reasonably expected to be useful. In addition, the cited prior art provide additional motivation to employ calcitriol in the instant treatment method because it is known that atopic keratoconjunctivitis is a T-cell inflammation prominent disorder and may lead to infiltration and corneal involvement such as epithelial keratitis. Therefore, employing any T-cell proliferation inhibitor, including calcitriol, would have been reasonably expected to treat keratoconjunctivitis and keratitis, including phlyctenular keratitis or corneal infiltration, thereby.

Furthermore, one of ordinary skill in the art would have motivated to employ calcitriol in a method to inhibit interleukin-1 production in cornea epithelium and thereby treat ocular inflammation because calcitriol is known to inhibit the production of interleukin-1α at a presecretory level by reducing the level of interleukin-1α mRNA. One of ordinary skill in the art would therefore reasonably expect calcitriol be useful in inhibiting the production of interleukin-1 and reducing the function of LC and LC induced activation of T cells, thereby decreasing the inflammation response and treating ocular inflammation.

Response to Arguments

Applicants' rebuttal arguments averring no motivation is being provided by the cited prior art to direct one of ordinary skill in the art to employ the herein

claimed vitamin D compounds in inhibiting LC in the eye have been considered, but are not found persuasive. As discussed above, calcitriol is known to inhibit the production of TNF-α, which is known to induce LC migration in the skin. Therefore, employing the very same compound to inhibit LC migration in the eye would have been reasonably expected to be effective, absent evidence to the contrary.

Applicant's remarks with regard to the herein claimed compounds can treat the herein claimed inflammation without lowering the transparency of the cornea have been considered but are not found persuasive because firstly it is not clear how such effect is relevant to the basis of rejection under 35 USC 103(a). And secondly argument drawn to unclaimed limitations are considered moot.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will

the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (703) 305-1002. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (703) 305-1877. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

San-ming Hui
Patent Examiner
Art Unit 1617
April 1, 2003